UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,986	07/01/2002	Seishi Nagamori	56972 (71526)	2684

21874 7590 06/04/2007

EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
HORNING, MICHELLE S	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
06/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/049,986	NAGAMORI, SEISHI	
	Examiner	Art Unit	
	Michelle Horning	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to communication filed 3/5/2007. The status of the claims is as follows: claims 1-20 are canceled and claims 21-29 are under current examination.

Claim Rejections-WITHDRAWN

The following rejections have been withdrawn due to claim amendments and persuasive arguments made by the Applicant.

1. 35 USC 112, 2nd paragraph;

2. 35 USC 103 (11/097, 994 and Carloni et al); and

3. 35 USC 103 (11/097, 994 and Akoi et al).

Claim Rejections-NEW

35 U.S.C. 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the FLC-4 cell line at best, does not reasonably provide enablement for any and all human hepatocytes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims. Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)).

Nature of invention. The claims are drawn to a method of HCV proliferation.

State of the prior art. Aoki et al (1998) disclose that although some lymphocyte cell lines have been shown to support partial replication of HCV, "there are currently no efficient *in vitro* systems yet to grow HCV" (See Introduction). This reference examines various mammalian cells and found that one human hepatoma cell line supported efficient expression of HCV minigene RNA (See Introduction). The FLC4 cell line increased both the stability and the translational efficiency of the RNA (see Discussion).

In addition to the teachings of Aoki et al, post filing art by the inventors state the following recitation: "The use of FLC4 cells may contribute to the success of this system. We have previously shown that this cell line supports efficient HCV structural gene expression by a recombinant adenovirus vector (Aoki et al., 1998). The results of this report also suggest that some host factors which increase the efficiency of translation of HCV minigene RNA are present in FLC4, but not other cells, including several commonly used human hepatoma cell lines (Aizaki et al., 2003)."

Breadth of the claims. The claims are broad, encompassing any and all hepatocyte cell lines.

Working examples. The working examples (1 and 2) are specifically drawn to the FLC4 cell line.

Guidance in the specification. There is absolutely no guidance in the application regarding the use of other hepatoma cell lines with the claimed method.

Predictability in the art. One could reasonably expect low success using other cell lines with the claimed method; however, there is no way one could predict the actual outcome of this method with other cell lines, given the prior art suggests that after examining various mammalian cell, only the FLC4 cells could support efficient expression of HCV minigene RNA (see above).

Amount of experimentation necessary. It would require much additional experimentation of any and all cell lines to ultimately achieve a successful method of HCV proliferation as claimed.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the full scope of the claimed methods.

35 U.S.C. 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawada, Nagamori et al. (hereinafter as "Kawada et al.", 1998) and Aoki et al. (1998). The limitations of the rejected claims are as follows: a method for proliferating a hepatitis C virus, characterized by providing

a porous carrier capable of immobilizing human hepatocytes thereon which is placed in a culture vessel capable of generating a continuous stream of a liquid culture medium in the culture vessel; immobilizing human hepatocyte cells on the porous carrier by introducing a continuous stream of liquid medium comprising the human hepatocyte into the culture vessel; infecting the immobilized human hepatocyte cells with a hepatitis C virus, an infectious clone RNA thereof, or a combination thereof; and proliferating the hepatitis C virus in the immobilized human hepatocyte cells in the continuous stream of liquid medium; wherein the carrier is a particulate porous carrier; wherein the hepatocyte is an established cell line; wherein the culture vessel is a radial flow bioreactor; wherein the cell line is the FLC4 line; wherein no additional supply of fresh culture medium is introduced to the culture vessel after the HCV is added to the medium; and wherein the human hepatocyte proliferates in three dimensions.

Aoki et al. teach an *in vitro* system that successfully supports the efficient growth of HCV via the FLC4 cell line. This cell line in particular exhibited very high reporter gene expression with pT7HCVLuc in comparison to the low success rates of various other cell lines (see Abstract). Aoki et al. teach that the combination of the HCV minigene with the FLC4 cell line is "useful to study the virus-cell interaction of HCV infection and other viruses for which there are no efficient in vitro replication systems" (see Introduction). These cells, however, were infected in a 12-well plate and the inocula were removed after one hour of incubation followed by medium replacement (see page 147 in Materials and

Methods); thus, Aoki et al. do not disclose the use of a radial flow reactor for the proliferation of HCV.

Kawada et al. discloses a support system employing a highly functional liver cell line cultured in a radial flow bioreactor and compared the cells to those grown in a conventional monolayer culture (see Summary). The radial flow bioreactor consists of a matrix comprised of porous glass bead microcarriers to which cells attach and proliferate throughout the matrix (see Results). Using the disclosed three-dimensional culture leads to the cell's natural morphology and function. The continuous flow through the matrix generates a beneficial concentration gradient of oxygen and nutrients while preventing excessive shear stresses or build up of waste products (see Introduction). Further, conditions resembling the *in vivo* state can be achieved (see Introduction).

Given the reasons above, it would have been obvious to one of ordinary skill in the art to combine the teachings of Aoki et al. and Kawada et al. in order to come up with a successful method of proliferating HCV. One would have been motivated to use this system as opposed to the conventional culture system utilized by Aoki et al. for the reasons below as suggested by Kawada et al. Conventional culture systems lead to 1. short culture lifespan and insufficient cellular function and productivity due to poor culture environment, 2. insufficient cell density, and 3. difficulty to scale-up culture processes (see Discussion). There would have been a reasonable expectation of success given that FLC4 cells exhibits very high reporter gene expression of HCV as disclosed by Aoki et

al. and the use of the described bioreactor system results in healthy liver cells that perform at naturally functioning levels. While neither reference teaches infecting liver cells with HCV in a continuous flow media, there would still be a reasonable expectation of success given that Aoki et al successfully infected cells by merely adding the virus innocula to the cells (see page 147 in Materials and Methods). Kawada et al. teach that the free flow of the liquid media throughout out the matrix provides an even distribution of oxygen and nutrients (see Results) and the even distribution of virus in the media would also be expected. The cells in the radial flow bioreactor were both spherical and covered with microvillilike processes (see Summary), which would lead to a greater surface area being exposed to the added virus in the media as opposed to the flattened cells in the conventional monolayer system.

The claims are rejected because the prior art teaches that HCV translation in the FL4C cell line is successful while in other cells, it is not. And, the radial flow bioreactor system provides an optimal environment for heptocytes in maintaining their natural morphology and function as opposed to the conventional monolayer system. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

CONCLUSION

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michelle Horning whose telephone number is 571-272-9036. The examiner can normally be reached on Monday-Friday, 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 570-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for unpublished application is available through Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michelle Horning
Patent Examiner

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600